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Article

Real-World Data Analysis of Patients Affected by Acquired Thrombotic Thrombocytopenic Purpura in Italy

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Abstract: The therapeutic management of acquired thrombotic thrombocytopenic purpura (aTTP) has recently benefited from the introduction of caplacizumab, an agent directed to inhibition of platelet aggregation. This real-world analysis investigated the epidemiology, the demographic and clinical characteristics of aTTP patients in Italy before and after caplacizumab introduction in 2020. Hospitalized adults with aTTP were included using the administrative databases of healthcare entities covering 17 million residents. Epidemiological estimates of aTTP considered the 3-year period before and after caplacizumab introduction. After stratification by treatment or not with caplacizumab, aTTP patients were characterized for their demographic and clinical features. The annual incidence before and after 2020 was estimated in the range 4.3-5.8 cases/million and 3.6-4.6/million, respectively. From 2018 to 2022, 393 patients with aTTP were included, 42 of them treated with caplacizumab. Caplacizumab-treated patients were aged on average 46.8 years, 31% were males, and showed tendentially better clinical outcomes: no treated patients died at either 1 month or 3 months after caplacizumab treatment initiation, compared to 10.5% (1 month) and 11.1% (3 months) mortality among the untreated. Caplacizumab treatment was associated with a trend towards shorter hospital stays. These findings suggest that caplacizumab advent provided clinical and survival benefits for patients with aTTP.

Keywords: acquired thrombotic thrombocytopenic purpura; caplacizumab; epidemiology; mortality; real-world evidence

1. Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare blood disorder characterized by clotting in small blood vessels that leads to thrombocytopenia and hemolytic anaemia [1]. TTP is caused by congenital (cTTP) or by acquired immune-mediated (aTTP) deficiency/absence of von Willebrand factor (VWF)-cleaving protease ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13), leading to platelet consumption in VWF-platelet aggregates and ultimately microvascular thrombosis [2]. The formation of microthrombi results in end-organ ischemia and damage, with central nervous system (CNS), heart and kidneys as the most injured organ systems [1]. If untreated, aTTP can be a fatal disease in approximately 90% of the cases, but therapeutic interventions can dramatically decrease mortality rates to 10-15% [3].

Historically, aTTP has been managed by plasma exchange (PEX) [4] and immunosuppressive therapy [5–7]. The therapeutic options for aTTP patients have recently been enlarged by the introduction of caplacizumab, a new anti-VWF humanized single-variable domain immunoglobulin (nanobody), able to inhibit VWF-platelet aggregation. The effectiveness of caplacizumab has been

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compared with placebo plus standard of care and glucocorticoids in two double-blind trials, TITAN and HERCULES [8,9]. The results of TITAN trial, published in 2016, reported higher rates of relapses in the intervention arm one month after termination of caplacizumab, possibly due to unsolved autoimmune activity [8]. Successively, the HERCULES trial extended the length of caplacizumab treatment over 30 days after PEX depending on the recovery of ADAMTS13 activity, resulting in a marked decrease in the occurrence of relapses. Moreover, a lower incidence of the composite outcomes of aTTP-related death, recurrence of aTTP, or thromboembolic event was found in caplacizumab arm compared to placebo (12% vs 49%; $p<0.001$) [9]. In view of the positive results of these RCTs, caplacizumab was approved in Europe for the treatment of aTTP in August 2018 [10] and then approved for reimbursement in Italy in January 2020 [11].

While clinical trials are meant to provide data from highly controlled subjects and protocols in terms of drug administration, real-world evidence (RWE) studies might give precious additional information from daily clinical practice on unselected patients, especially considering the potential influence of factors, like location, compliance, comorbidities, and concomitant treatments. To date, RWE studies conducted in Germany, France and Spain have suggested that the advent of caplacizumab brought significant clinical and economic benefits over the traditional therapy, mainly attributable to reduced time to platelet count normalization, duration of PEX [12], risk of an exacerbation or relapse after the initial therapy [13], shortened hospital stay [12–14], and noticeably reduced mortality [13,14].

In Italy, there is poor evidence on the epidemiology of aTTP, and the results of the introduction of caplacizumab treatment on large populations outside clinical trials are lacking. The present real-world analysis aimed at estimating the epidemiology of patients with aTTP in Italy, to describe their demographic and clinical characteristics before and after the advent of caplacizumab.

2. Materials and Methods

2.1. Data Source

An observational retrospective analysis was performed using data retrieved from the administrative databases of sample of Italian healthcare entities covering nearly 17 million health-assisted individuals (corresponding to approximately 29% of the entire country population). The participating Local Health Units were selected by geographical distribution (by North/Centre/South Italy), by data completeness, and by the high-quality linked datasets. The selected healthcare entities belonged to 11 Italian Regions (i.e. Veneto, Piedmont, Lombardy, Liguria, Umbria, Lazio, Abruzzo, Molise, Apulia, Campania, and Sicily). The following databases were used: beneficiaries' database, to get information on patients' demographics and date of death; pharmaceuticals database, to collect data on drug prescriptions, including the anatomical therapeutic code (ATC), date of prescription, number of packages; hospitalization database, to obtain all data related on hospital admissions, namely date of hospitalization, main and secondary diagnosis identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and Diagnosis Related Group (DRG); outpatient specialist service database to gather information about laboratory test, specialist visits with type and date of provision. In order to ensure privacy, an anonymous univocal numeric code (Patient ID) was given to each participant in the analysis. The patient ID allowed the electronic linkage between databases and also warranted the anonymity of the extracted data in full compliance with UE Data Privacy Regulation 2016/679 ("GDPR") and Italian D.lgs. n. 196/2003, as amended by D.lgs. n. 101/2018. All the findings were presented as aggregated data, so that they could not identify, either directly or indirectly, individual patients. The analysis was conducted in line with the principles of the Declaration of Helsinki and approved by the local Ethics Committees of the participating healthcare entities.

2.2. Study Design and Patient Population

From a sample population of almost 17 million health-assisted individuals, hospitalized adult (≥18 years) patients with a diagnosis of aTTP were identified by the ICD-9-CM code 446.6 between

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January 2018 to end of data availability (up to March 2023, inclusion period). Women with complications of pregnancy identified by the codes ICD-9-CM 634–639 (other pregnancy with abortive outcome) and ICD-9-CM 640–649 (complications mainly related to pregnancy) were excluded from the analysis. Moreover, patients treated with caplacizumab were identified by the presence of at least one prescription for caplacizumab (ATC B01AX07). The group untreated with caplacizumab consisted of patients with aTTP without a prescription for caplacizumab, by considering all the available observational period. The index-date was the time of the first prescription of caplacizumab for the treated cohort and the time of first hospitalization with aTTP discharge diagnosis (throughout the whole inclusion period) for the caplacizumab-untreated cohort. The characterization period was all the time of data availability preceding the index-date and the follow-up was all the available period after the index-date.

For all patients with aTTP, demographic variables in terms of age, distribution of subjects below or over 50 years of age, and gender (proportion of males) were recorded at inclusion. Comorbidity profile was assessed during the characterization period using the Charlson Comorbidity Index, a score resulting from the sum of weight assigned to 19 concomitant conditions, thus 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity [15]. Moreover, the mean number and the mean duration of aTTP-related hospitalization before the index-date (if any) were collected.

2.3. Annual Incidence of aTTP

The annual incidence of aTTP was estimated during a 6 years' time-horizon, covering 3 years before (2017, 2018, 2019) and after (2020, 2021, 2022) caplacizumab introduction into the Italian market. The annual incidence was calculated as the number of patients hospitalized for aTTP and reported as cases per million people.

2.4. Statistical Analysis

All the analyses were purely descriptive. Continuous variables are reported as mean ± standard deviation (SD) and median and interquartile range (IQR, 25° and 75° percentile); categorical variables are expressed as frequencies and percentages. Patients were divided into treated and untreated with caplacizumab. For the untreated cohort, a propensity score matching (PSM) was applied to select a subgroup of patients comparable with caplacizumab-treated ones, for demographic age, clinical characteristics (i.e. Charlson comorbidity Index), and the mean number/patient of aTTP hospitalization prior the index-date. All data were reported as descriptive for caplacizumab-treated cohort and caplacizumab-untreated cohorts, PSM matched and unmatched.

Following the 'Opinion 05/2014 on Anonymization Techniques' drafted by the 'European Commission Article 29 Working Party', the analyses involving fewer than three patients were not reported, as they were potentially traceable to single individuals. Therefore, the results referring to <4 patients were not reported. All analyses were performed using STATA SE version 17.0 SE (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Annual Incidence of aTTP Hospitalization and Projection to the Italian Population

The estimated annual incidence (defined as the annual number of patients hospitalized with aTTP diagnosis) before the introduction of caplacizumab was 4.3 cases/million in 2017, 4.5 cases/million in 2018 and 5.8 cases/million in 2019; instead after the introduction of caplacizumab in the clinical practice, there were 4.4 cases/million in 2020, 3.6 cases/million in 2021 and 4.6/million in 2022 (data not shown).

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3.2. aTTP Patients Treated with Caplacizumab: Baseline Patients Characteristics and Outcomes

Across 2018-2022, overall 393 patients with aTTP were included in the study, of whom 42 received caplacizumab. The age at index-date (first prescription of caplacizumab) averaged 46.8 ± 11.4 years (median age: 48.5 years), and 31% were males. Patients treated with caplacizumab were a relatively young population with 57.1% of patients aged below 50 years and with a mild comorbidity profile documented by a mean (± SD) Charlson Comorbidity Index of 0.6 (± 0.8) and a median Charlson Comorbidity index of 0.0. In this cohort, a mean number of previous aTTP hospitalizations of 0.9 ± 1.7 (median: 0.0) per patient, and a mean duration of previous aTTP hospitalization (calculated only in previously hospitalized patients) of 15.8 ± 12.0 days (median: 12.5 days), were found during all available period before caplacizumab therapy initiation (mean duration 9.5 ± 3.7 years). By considering a mean follow-up period of 13.5 months, some major endpoints were evaluated. In patients treated with caplacizumab, no deaths (0/42) were recorded after 1 month and 3 months from the first prescription, and the mean duration of hospital stay in the ordinary setting (for any cause and evaluated up to one-year follow-up) was 15.7 ± 11.1 days (median: 13.0 days). Among 42 patients treated with caplacizumab, <4 patients (<9.5%) were admitted to ICU during the first year of follow-up (including the index-date), thus not allowing to report the mean duration of ICU hospitalization due to data privacy reasons (sample size <4 patients). Among all 42 patients treated with caplacizumab, the overall duration of the ICU hospitalization was <4 days. By considering the entire follow-up period available, the number of caplacizumab vials prescribed averaged 31.2 ± 20.3 per patient (median: 29.0 vials).

3.3. Propensity Score Matching Adjusted aTTP Patients Untreated with Caplacizumab: Baseline Characteristics and Outcomes

After PSM with 1:4 ratio (between patients treated with caplacizumab and patients with aTTP untreated), 168 patients with aTTP and untreated with caplacizumab were balanced for baseline characteristics with patients treated with caplacizumab and thus included in the analysis. The mean age was 47.5 years (median: 48.5 years), the Charlson Comorbidity Index averaged 0.6 (median: 0.0) and the mean number/patient of previous aTTP hospitalisation was 0.7 (median: 0.0). The mortality rate at 1 month after index-date was 8.9%, while at 3 months was 10.1%. The mean duration of ordinary hospitalisation was 30.3 ± 44.4 days (median: 15.0 days), while the mean duration of ICU hospitalisation was 9.4 days (median: 6.0 days; 207 days in total).

The baseline demographic and clinical characteristics, together with the descriptive analysis of clinical outcomes in aTTP patients treated and untreated with caplacizumab, before and after PSM are described in Table 1.

Table 1. Baseline characteristics and descriptive analysis of clinical outcomes in aTTP patients treated and untreated with caplacizumab, before and after PSM.

	Caplacizumab-treated patients (N=42)	**Caplacizumab-untreated patients, pre-PSM (N=351)**	**Caplacizumab-untreated patients, post-PSM (N=168)**
Patients' baseline characteristics			
Male gender, N (%)*	13 (31.0%)	156 (44.4%)	53 (31.5%)
Age at index-date, years, mean (SD)*	46.8 (11.4)	57.6 (17.5)	47.5 (15.0)
Age at index-date, years, median (IQR)	48.5 (40.2-53.8)	58.0 (45.5-71.0)	48.5 (36.0-57.0)
Age, year, min-max	(19-69)	(18-96)	(18-83)
Age <50 years, N (%)	24 (57.1%)	115 (32.8%)	90 (53.6%)
Age ≥50 years, N (%)	18 (42.9%)	236 (67.2%)	78 (46.4%)

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Charlson Comorbidity Index, mean (SD)*	0.6 (0.8)	1.6 (1.9)	0.6 (0.8)
Charlson Comorbidity Index, median (IQR)	0.0 (0.0-1.0)	1.0 (0.0-2.0)	0.0 (0.0-1.0)
Charlson Comorbidity Index = 0, N (%)	23 (54.8%)	112 (31.9%)	99 (58.9%)
Charlson Comorbidity Index ≥1, N (%)	19 (45.2%)	239 (68.1%)	69 (41.1%)
Number of previous aTTP hospitalizations, mean (SD)*	0.9 (1.7)	0.4 (1.5)	0.7 (2.0)
Number of previous aTTP hospitalizations, median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Length of previous aTTP hospitalization, days, mean (SD)	15.8 (12.0)	54.1 (74.3)	53.2 (73.6)
Length of previous aTTP hospitalization, days, median (IQR)	12.5 (9.0-16.5)	20.0 (11.8-58.0)	20.0 (12.0-54.0)
Length of available characterization period, years, mean (SD)	9.5 (3.7)	8.7 (4.0)	8.0 (3.9)
Outcomes			
Mortality at 1 months (after index-date), N (%)	0 (0.0%)	37 (10.5%)	15 (8.9%)
Mortality at 3 months (after index-date), N (%)	0 (0.0%)	39 (11.1%)	17 (10.1%)
Length of all-cause ordinary hospitalization[#], days, mean (SD)	15.7 (11.1)	29.0 (45.9)	30.3 (44.4)
Length of all-cause ordinary hospitalization[#], days, median (IQR)	13.0 (9.0-17.0)	16.0 (7.0-28.0)	15.0 (7.0-30.0)
Patients hospitalized in ICU[#], N (%)	<4 (<9.5%)	39 (11.1%)	22 (13.1%)
Length of ICU hospitalization[#], days, mean (SD)	NA	10.5 (13.2)	9.4 (9.4)
Length of ICU hospitalization[#], days, median (IQR)	NA	6.0 (1.0-15.0)	6.0 (2.2-17.0)
Overall duration of ICU hospitalization (all patients), days	<4	408	207
Number/patient of caplacizumab vials prescribed[§], mean (SD)	31.2 (20.3)	-	-
Number/patient of caplacizumab vials prescribed[§], median (IQR)	29.0 (14.2-39.8)		
Follow-up, months, mean	13.5	26.2	28.5

* variables considered for the propensity score matching, PSM; [#]up to one year after the index-date; [§] overall period. Abbreviations: NA, not accountable; IQR: interquartile range (25° and 75° percentile); SD, standard deviation.

4. Discussion

This analysis was undertaken primarily to fill the informative gap about the impact caplacizumab introduction into the daily clinical practice in Italy, and secondarily to assess the aTTP epidemiology data and characteristics of patients.

The current real-world analysis showed that at baseline patients treated with caplacizumab had a mean age of 46.8 years with 69% of patients being females. This population mirrored the data of existing literature, coming from both RCT analyses and European RWE, where among patients treated with caplacizumab a mean age of 45-46 years was found with 66-70% of patients being females [9,12–14]. The main clinical endpoints, such as all-cause mortality, hospitalizations, and ICU admissions, were analysed. One month after the index-date, 0% (0/42) and 10.5% (37/351) of mortality (for all-cause), respectively, was observed for patients treated and untreated with caplacizumab. In addition, the duration of all-cause hospitalization up to one-year follow-up averaged 15.7 days (median 13.0 days) for patients treated with caplacizumab and 29.0 days (median 16.0 days) for the untreated group. Besides, the mean duration of ICU stays among the cohort treated with caplacizumab was not reported for data privacy reasons, since the patients were less than 4, while in untreated cohort the duration of ICU stay averaged 10.5 days (median 6.0 days) per patient. As there were some differences in the two cohorts in terms of age, comorbidity profile and aTTP mean number of hospitalisations before the index-date, the analysis was also conducted with the application of a

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PSM that allows to minimize selection bias and to analyse a subgroup of untreated patients matched with treated ones. Matched untreated patients had a mean age of 47.5 years, comparable to 46.8 years of the group treated with caplacizumab; the Charlson Comorbidity Index was 0.6 in both groups and the mean hospitalisation before index-date was 0.9 and 0.7, respectively. Regarding the main clinical endpoints, the mortality rate at 1 month after index-date was 0% in patients treated with caplacizumab and 8.9% in untreated ones, while at 3 months was 0% and 10.1%, respectively. Our data are in line with the clinical trial HERCULES [9] and other European RWE analyses [12–14]. In the HERCULES trial, where the aTTP-related death was assessed during the treatment period (30 days), the aTTP-related mortality of caplacizumab-treated patients was 0% (0/72), compared to 4% (3/73) in the placebo-group [9]. Data from French observational analysis showed 1.1% death within 30 days since diagnosis in patients treated with caplacizumab and 6.7% of mortality among historical aTTP cohort included before the introduction of caplacizumab into French clinical practice [14]. Moreover, a recent Italian retrospective analysis carried out by using the Milan TTP Registry reported that among 26 patients treated with caplacizumab for an acute aTTP episode, all patients had a remission with 0% mortality rate [16].

The mean duration of ordinary hospitalisation was 15.7 ± 11.1 days (median 13.0 days) for patients treated with caplacizumab and 30.3 ± 44.4 days (median 15.0 days) for the untreated ones, while the mean duration of ICU hospitalisation was not reported since referred to <4 patients in patients treated with caplacizumab and 9.4 days (median 6.0 days) in untreated aTTP cohort. These data are consistent with previous evidence from the literature. Coppo et al. showed a median length of hospitalization of 13 days and 22 days for the cohort treated with caplacizumab and the historically untreated cohorts, respectively [14]. These results were also confirmed by Izquierdo et al. who reported a statistically significant difference in hospitalization days between patients treated and untreated with caplacizumab (12 days vs 19 days respectively, $p<0.001$) [12]. Moreover, Völker et al. described a mean hospitalization length of 21.6 days in patients treated with caplacizumab [13]. Similarly, the analysis of Milan TTP Registry indicated a median length of hospital stays for patients treated with caplacizumab of 18 days [16]. The therapy with caplacizumab implied a mean consumption of around 31 vials per patient during the overall observation period; data from Milan Registry and German RWE analyses showed a median duration of caplacizumab treatment of 26 and 34 days, respectively [13,17].

In our sample covering approximately 29% of the entire Italian population and belonging to 11 Italian regions, the mean yearly incidence of patients hospitalized for aTTP was 4.5 cases per million people, with an almost linear increase trend across 2017-2022. Moreover, the overall 2017-2022 increasing trend observed in aTTP diagnoses might be explained by several educational activities started across the country among interprofessional team for improving care coordination and communication to advance the diagnosis of aTTP. The epidemiological data on aTTP reported in this study are in agreement with the Italian data previously published by Istituto Superiore di Sanità (ISS) [18]. Besides, the incidence in Europe has been estimated to be between 1.5 and 6.0 cases per million [19–24], consistent with the current report.

The present results must be interpreted considering some current limitations related to the observational nature of the analysis, and the use of data extracted from administrative databases. The analysis was carried out among a sample corresponding to the 29% of the entire Italian population, belonging to 11 Regions, geographically distributed across the national territory. Thus, since the sample covers a limited number of healthcare entities, the results might suffer from an uncaptured of diversities in clinical practice settings. Moreover, one intrinsic flaw of administrative databases is that they are not originally meant to be used for research purposes, thus certain events and diagnoses might be incomplete or lacking. Administrative data are collected for reimbursement, not for coordinating medical care or conducting outcomes research, which could translate into incomplete information on disease severity, comorbidities, and other potential confounders that could have influenced the results. For instance, the Charlson Comorbidity Index was calculated using drug prescription and hospitalizations as proxies of diagnosis of each concomitant disease, therefore untreated or non-hospitalized comorbidities were not captured. For this reason, in the analysis, a

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control cohort of patients untreated with caplacizumab has been considered to overcome this bias, so uncaptured clinical features (e.g. the baseline clinical manifestations and baseline laboratory parameters) which could have influenced the outcome results, would affect both groups. In fact, for data interpretation, it should be considered that some clinical variables, such as the levels of ADAMTS13 and bleeding complications, were not captured among administrative databases.

Moreover, it is acknowledged that the data presented here are purely descriptive rather than the results of a randomized study, and no comparative analyses were presented among patients treated with caplacizumab and untreated ones. The study population comprising patients with aTTP was filtered from the health records using the ICD-9-CM classification diagnostic code, as previously reported [25,26], thus if patients were not classified as such in their health records with an established aTTP diagnosis, these were not included in the analysis.

Despite these shortcomings, administrative data have been widely used and have been generally successful in evaluating the association between disease conditions and clinical/economic outcomes. Another strength is represented by the large sample size of an unselected population in real-life settings, thus comprising patients (as elderly, or with a multimorbid profile) generally underrepresented in randomized clinical trials.

5. Conclusions

In conclusion, with respect to the previous retrospective analyses carried out by using data from the Milan TTP Registry collected from a unique centre of excellence [16,27,28], this is the first real-word analysis of aTTP from several healthcare districts in Italy after the introduction of caplacizumab into the clinical practice. Such approach could represent a powerful and necessary tool to systematically collect epidemiologic, clinical and laboratory data with a good representativeness of the Italian clinical practice. Therefore, this real-world analysis provided an up-to-date description of the current management of patients with aTTP, the results of treatments, as well as its epidemiology.

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Institutional Review Board Statement: This observational study was performed in accordance with the principles of the Declaration of Helsinki. This study has been notified and approved by the local Ethics Committee of the healthcare entities involved in the study.

Informed Consent Statement: According to the pronouncement of the Data Privacy Guarantor Authority (General Authorization for personal data treatment for scientific research purposes – n.9/2014, December 11th – published on the Official Gazette n. 301 on December 30th, 2014) data treatment is authorized without patient Informed Consent, when the collection is impossible due to organizational reasons.

Data Availability Statement: All data used for the current study are available upon reasonable request next to CliCon s.r.l. which is the body entitled of data treatment and analysis by the healthcare entities involved in the study.

Conflicts of Interest: Emanele Angelucci is DMC member for Bristol Myers Squibb, Vertex and Vifor, consultant for Menarini-stemline and Sanofi, member of the Advisory board for Roche, Novartis, Gilead, Regeneron, speaker for Novartis, Gilead, Sanofi; Andrea Artoni received honoraria as Advisory Board from SANOFI; Luana Fianchi declares consulting fees from Sanofi, Bristol Myers Squibb and Jazz Pharmaceuticals. All the other authors have no competing interest to disclose.

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